REMARKS

Claims 19-39 were previously pending in this application. Claims 19-39 are still pending for examination with claim 19 being an independent claim. No claims have been amended, canceled or added. No new matter has been added.

Objection to Information Disclosure Statement (IDS)

The Examiner has requested a list of co-pending applications as well as a copy of the references cited in co-pending Application No. 08/738,652, now with the Board of Interferences. A list of co-pending applications and the references cited in Application No. 08/738,652 will be submitted. Applicants respectfully request that the Examiner consider each of the references and return an initialed copy of the 1449 to Applicants.

Double Patenting Rejection

The Examiner rejected Claims 19-39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,239,116. Claims 19-39 were not obvious at the time of the invention over claims 1-19 of U.S. Patent No. 6,239,116 because claims 1-19 of U.S. Patent No. 6,239,116 do not suggest that the CpG oligonucleotide be administered to a subject having asthma. Claims 1-19 of the '116 Patent are directed to a method for inducing IL-6 in a subject. The claims of the '116 Patent do not include any reference to allergens or asthma. The currently pending claims, by contrast, include the limitation that the CpG oligonucleotide is administered to a subject to treat asthma. In the most recent Office Action, the Examiner objected to this distinction, stating that "the pending claims do not specifically recite that the subject has asthma." Applicants respectfully disagree. The preamble to Claim 19 specifies that the claim is "[a] method for treating asthma." It is not possible to "treat asthma" on a subject that does not have asthma. It would be clear to one of ordinary skill in the art that Claim 19 (and its dependent claims) necessarily relates to a subject that has asthma. Accordingly, Applicants respectfully request the Examiner reconsider the double patenting rejection with respect to claims 1-19 of the '116 Patent.

Provisional Double Patenting Rejections

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102, and 103 of co-pending U.S. Serial No. 09/337584. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 09/337584 application have been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 46, 52, 64, 71, 72, 74, and 80 of co-pending U.S. Serial No. 10/613739. According to the Examiner, the claims are not patentably distinct from one another. The rejection is a provisional one since none of the claims in the 10/613739 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 22, 23, 31, 32, and 34-37 of co-pending U.S. Serial No. 10/769282. According to the Examiner, the claims are not patentably distinct from one another. The rejection is a provisional one since none of the claims in the 10/769282 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 19-29 and 31-33 of co-pending U.S. Serial No. 10/894862. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 10/894862 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 42, 45-53, and 57-60 of co-pending U.S. Serial No. 09/337893. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 09/337893 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Rejection under 35 U.S.C. § 112 ¶ 1

Claims 19-39 have been rejected under the first paragraph of 35 U.S.C. § 112 for lack of enablement. The Examiner has indicated that a method for treating asthma using SEQ ID NO. 10 to treat a murine subject is enabled but that the use of other CpG containing oligonucleotides is not enabled. Applicants request reconsideration in light of this response.

The Examiner stated that examples of induction of interleukins in spleen, liver, or thymus cells are not representative of successful treatment of asthma using any CpG containing oligonucleotide because the specification does not teach a correlation between in vitro IL-6 induction and *in vivo* asthma treatment. (Office Action Pages 17-18.) Applicants respectfully disagree. The specification does teach that redirecting immune response from Th2 to Th1 is useful in the treatment or prevention of asthma. For example, on Page 8 Lines 11-13, the specification states that "by redirecting a subject's immune response from Th2 to Th1, the instant claimed nucleic acid modules can be administered to treat or prevent the symptoms of asthma." The specification also teaches that Th1 cytokines can suppress the formation of Th2 clones, and that Th2 clones are known to be elevated in asthmatic subjects. See Page 41 Lines 33-38. Accordingly, the specification does teach a correlation between in vitro IL-6 induction and *in vivo* asthma treatment.

The examiner has cited McCluskie et al 1999 (Molecular Med. 1999, 5/5:287-300) for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. (Office Action Pages 20-21.) Applicants responded that McCluskie is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines). The examiner responded that the claims "do not specifically exclude plasmids, vectors, or DNA vaccines. The immunostimulatory nucleic acid could read on the whole bacteria, or [...] could be part of a DNA vaccine." (Office Action Pages 20-21.)

McCluskie discusses the variable therapeutic effectiveness of DNA vaccines wherein a plasmid is introduced into non-human primates and mice. The plasmid DNA in McCluskie encodes a particular antigen, namely either the middle or major surface protein of the hepatitis B virus. (See Page 289.) The immunity mechanism discussed in McCluskie relates to the expression of that antigen to generate an immune response. By contrast, the pending claims do not relate to DNA encoding a particular antigen to which an immune response is desired. The pending claims describe the use of an oligonucleotide, which is not a plasmid. Additionally, the key feature of the pending claims is the CpG motif, not a DNA sequence encoding a particular protein antigen. The variable therapeutic response discussed in McCluskie concerns the immune response to the antigen (surface proteins from the hepatitis B virus) and is thus not relevant to the enablement of the pending claims which concern shifting immune response from Th2 to Th1 to treat asthma. McCluskie does not show unpredictability of the latter effect (shift from Th2 to Th1), only the former (immune response to plasmid DNA encoding antigen). Applicants respectfully request that the Examiner reconsider the enablement rejection in light of this distinction.

The Examiner has cited Krieg et al 2000, Wohlleben et al 2001, Kline et al 2002, Kline et al 1998, Weiner et al 2000, Agrawal et al 2000, Satoh et al 2002, Dziadzio et al 2004, Barnes 2000, and Van Uden et al 1999 for the proposition that the state of the art is unpredictable with respect to the effectiveness of the claimed method. In response, Applicants provided a detailed explanation for each reference as to why the reference actually shows that the claimed method is promising as a treatment for asthma and that none of the references show that CpG oligonucleotides would be unsuitable for treatment of asthma. The Examiner responded that "even though these references may suggest the possibility if CpG's usefulness in treating a subject having asthma, they still also indicate even several years after Applicants' effective filing date that the scope of the claimed method is not enabled." (page 21.) Applicants respectfully submit that the Examiner has not met the burden of showing lack of enablement. The Examiner did not respond to Applicants' explanations as to why none of the references showed that CpG oligonucleotides would be unsuitable or unpredictable as an asthma treatment, instead the Examiner only stated that the references indicated the claims were not enabled. Applicants request the Examiner reconsider

Applicants' explanations in response to the July 6, 2005 Office Action which show that none of the above-cited references indicate any lack of enablement.

In response to the July 6, 2005 Office Action, Applicants pointed out that several Phase I and Phase II human studies using subcutaneously administered CpG oligonucleotides have been performed to date in cancer trials, and that those studies demonstrate that CpG oligonucleotides, even in aggressive doses, are well tolerated by humans. The Examiner responded that the trials in question were for cancer, while the pending claims are directed to treatments for asthma and allergy, not cancer. Applicants submit that the evidence of human tolerance in the Kim et al 2004 abstract are, in fact, relevant to the safety of the methods encompassed by the pending claims regardless of the ultimate purpose of the CpG oligonucleotide treatment. Kim et al 2004 shows that CpG oligonucleotides are well tolerated by humans. That result does not depend on the therapeutic purpose of the CpG treatment. If CpG oligonucleotides are well tolerated when administered to a cancer patient, there is no reason to expect adverse effects when the oligonucleotides are administered to an asthmatic patient. Accordingly, Kim et al is relevant evidence of the safety of the claimed methods.

Applicants also pointed to a number of post-filing studies that further confirm the working examples in the pending application. Those studies reiterate, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. The Examiner stated that these studies were evidence of post filing. Applicants submit that the post-filing evidence was presented simply to rebut the Examiner's post-filing evidence of lack of enablement. Applicants do not rely on any of the post-filing references to provide enablement.

The Examiner also states that not every CpG oligonucleotide will be effective, and asks whether the *in vivo* data from one CpG molecule, SEQ ID NO: 10, indicate that all other CpG molecules will function to treat asthma. The data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) 1984, however, the court stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856,

858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims.

The specification teaches that, both *in vitro* and *in vivo*, CpG containing oligonucleotides drive the immune system toward a Th1 response, and thus constitute an effective asthma treatment. This is sufficient to enable the claimed methods. Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 – page 54, line 5) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention.

Applicants have presented a significant amount of data in the specification and asserted on the record that such data correlates with the scope of the claimed invention. Applicants have included many examples in the specification including induction of cytokines such as IL-6, IL-12 and IFN-gamma. The data in the application, includes that represented in Tables 1-3, which establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has the characteristic pattern of a Th1 response. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG containing oligonucleotides. The combination of these changes in immune parameters was adequate to demonstrate to one of skill in the art at the time of the filing of the priority patent application that CpG oligonucleotides would be useful in the treatment of asthma. Applicants assert that a correlation between CpG and their use in the treatment of asthma is disclosed and enabled.

MPEP section 2164.02 teaches that

> "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation

> and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
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> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

Applicants have presented data and asserted that it correlates with the scope of the claimed invention. The Examiner has not presented any objective evidence to demonstrate why it does not correlate.

Rejection under 35 U.S.C. § 112 ¶ 2

The Examiner stated that the claims are vague and indefinite in the recitation of "immunostimulatory oligonucleotide." Applicants respectfully disagree. Applicants define "immunostimulatory nucleic acid molecule" in the specification on Page 14. An "immunostimulatory nucleic acid molecule" refers to a nucleic acid molecule, which contains an unmethylated cytosine, guanine dinucleotide sequence (i.e. "CpG DNA" or DNA containing a cytosine followed by guanosine and linked by a phosphate bond) and stimulates (e.g. has a mitogenic effect on, or induces or increases cytokine expression by) a vertebrate lymphocyte. The specification also provides that "preferably the immunostimulatory CpG DNA is in the range of between 8 to 40 base pairs in size if it is synthesized as an oligonucleotide." Applicants submit that, in light of the specification and the limitation that the immunostimulatory oligonucleotide comprises an immunostimulatory motif comprising a 5'-cytosine-guanine-3', the term "immunostimulatory oligonucleotide" is not vague or indefinite.

Applicants also respectfully disagree that Claim 37 and Claim 38 lack antecedent basis. Neither Claim 37 nor Claim 38 includes a limitation that makes reference to an antecedent term. Applicants request the Examiner either withdraw these rejections or clarify why Claims 37 and Claim 38 lack antecedent basis.

Joint Inventorship under 37 CFR 1.56

The Examiner advises Applicants of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made. Applicants respond that all claims were commonly owned by the joint inventors at the time any inventions covered therein were made.

Rejection under 35 U.S.C. § 103 over McMichael and Pisetsky

Claims 19-25, 28, 30, 31 and 39 have been rejected under 35 U.S.C. §103 as being obvious over U.S. Patent No. 5,726,160 (McMichael) taken with Pisetsky (J. Immunology, 1996, pp. 421-413, *incorrectly listed in office action as published in 1995*).

According to the Examiner, McMichael teaches that "a composition comprising prokaryotic DNA and a pharmaceutically acceptable carrier can be used to treat subject suffering from pulmonary disease and specifically an asthmatic subject (col.1; col. 4, example IX)" and that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the bacterial CpG oligonucleotides as taught in Pisetsky, since the art teaches that the bacterial DNA has immunological properties, for administration to an asthmatic subject as taught in McMichael to treat pulmonary disease (asthma)." (Office Action Pages 15-16).

The combination of McMichael and Pisetsky does not produce the claimed invention. Neither McMichael nor Pisetsky teach a method for treating asthma. Although the Examiner has asserted that McMichael teaches a method for treating a "subject suffering from pulmonary disease and specifically an asthmatic subject," McMichael does not specifically teach treating an asthmatic subject. McMichael teaches that DNA can be used to treat a pulmonary disorder, "including cystic fibrosis, emphysema, chronic bronchitis, sinusitis, and the common cold." (Column 1 Lines 11-14.) The Examiner has pointed to Example IX for support. Applicants disagree that Example IX demonstrates treatment of an asthmatic subject. Example IX involves the treatment of a 58 year old woman having persistent adult rhinitis and sinusitis. It is noted in the Example that the woman had a childhood history of asthma. However, there is no indication that the woman currently had asthma and the Example specifically teaches that she had a different disorder, persistent adult rhinitis and sinusitis. There is no suggestion in McMichael that the therapies described therein

would find utility in the therapeutic treatment of asthma. Additionally, there is no teaching in Pisetsky that DNA could be useful for the treatment of asthma. Thus, the claimed invention was not obvious at the time of the invention in view of McMichael and Pisetsky.

Additionally, one of skill in the art would not have combined the teachings of Pisetsky and McMichael as suggested by the Examiner. There are at least two scientific distinctions between the teachings of Pisetsky and McMichael that would prevent the combination by one of ordinary skill in the art. Initially, McMichael teaches that DNA may be used to treat pulmonary disease. Although McMichael indicates in column 1 that the DNA may be prokaryotic or eukaryotic, all ten Examples involve the use of eukaryotic DNA (calf thymus DNA) and according to column 2 lines 28-29 are the "preferred embodiments of the invention." In contrast, Pisetsky teaches, as pointed out by the Examiner, that there is "compelling evidence that bacterial DNA, in contrast to mammalian DNA, can induce a variety of responses in both normal humans as well as animals." According to Pisetsky, mammalian, or eukaryotic DNA, does not stimulate the immune system but bacterial DNA, or prokaryotic DNA, does stimulate an immune response. Thus, Pisetsky teaches that only bacterial DNA can be used to stimulate an immune response and McMichael teaches that any DNA works but that mammalian DNA is preferred for reducing mucus viscosity. One of skill in the art would find these teachings to indicate different mechanisms of action and would not combine the references.

Secondly, Pisetsky teaches that bacterial DNA induces an immune response such that B and T cells are activated, macrophage are stimulated, antibody production is induced and cytokine production is induced (Page 422, left column, 1st full paragraph). There is no suggestion in Pisetsky that bacterial DNA or CpG oligonucleotides produce a Th1 biased response, reduce eosinophil accumulation, decrease IgE production or any other physiological parameters that would be associated with the successful treatment of a respiratory disease such as asthma. The only therapeutic uses for bacterial DNA or CpG oligonucleotides suggested or implied by Pisetsky are for cancer, viral, and bacterial disease. One of skill in the art reading Pisetsky would not expect that DNA which stimulates an immune response would be useful for treating pulmonary disease associated with increased mucus viscosity. McMichael, on the other hand, describes the use of DNA to decrease the viscosity of mucus secretions for the treatment of pulmonary disorders. One

of skill in the art would not be motivated to substitute an immune stimulating DNA, as described in Pisetsky, for the mucus viscosity decreasing mammalian DNA of McMichael to treat the pulmonary disorders of McMichael, particularly when the two described mechanisms are so different. Any suggestion that one of skill in the art would substitute the Pisetsky DNA for the McMichael DNA in the McMichael method would be based on hindsight.

Applicants reiterate on the record that pending claims 26-27, 29, and 32-38 have not been rejected in view of the prior art.

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

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